Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for the amendments to claims 1 and 29 may be found, *inter alia*, at pages 8-9, 15-20, and in Example 1 at pages 28-30; and support for the amendments to claim 6 may be found at page 16, lines 23-28. Accordingly, the present amendments do not add new matter, and their entry is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 33, 35, 36, 40, 44, 45, 49, 51 and 53 have been canceled as being drawn to non-elected restriction groups, and claims 1, 6 and 29 have been amended. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, 32 and 41-43 are pending in the application, with claims 1 and 41 being the independent claims.

III. Summary of the Office Action

In the Office Action dated May 11, 1999, the Examiner has made two rejections of the claims. Applicants respectfully offer the following remarks to overcome these rejections.

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IV. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Traversed

In the Office Action at pages 2-3, sections 3-4, the Examiner has rejected claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29 and 31-32 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse these rejections.

A. The Recitation of "Under Conditions Sufficient To"

In making this rejection, the Examiner first contends that the claims are indefinite because of the recitation of "under conditions sufficient to" in claims 1 and 29. Specifically, the Examiner contends that:

> It is not clear whether the same polymerase or reverse transcriptase as mentioned in claims 1(a) is involved in the condition to make a first nucleic acid molecule or there is an additional enzyme used. It is suggested to clarify uncertainty.

Office Action at page 2, section 4(a), line 2, through page 3, line 2. Applicants respectfully disagree with these contentions. Step (a) as recited in both claims 1 and 29 refers either to "mixing" one or more templates and one or more polypeptides (claim 1) or "contacting" the template(s) with one or more polypeptides (claim 29). Hence, it is clear from the plain language of these claims that a mixture of templates and polypeptides is subjected to the "conditions sufficient to" produce a product nucleic acid molecule in the subsequent steps recited in these claims. Therefore, Applicants respectfully assert that one of ordinary skill could easily determine the meaning of "under conditions sufficient to" as recited in the claims. However, to expedite prosecution and at the suggestion of the Examiner, claims 1 and 29 (and hence the remaining claims that depend therefrom) have been amended to indicate that step (a) in each of these claims results in the production of "a mixture," and it is this mixture that is then incubated "under conditions sufficient to" produce a nucleic acid molecule in the subsequent steps recited in these

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claims. As noted above, these amendments are fully supported in the specification as originally filed. Hence, Applicants respectfully assert that one of ordinary skill could readily determine the "conditions sufficient to" produce a nucleic acid molecule as recited in claims 1 and 29 as currently presented, based on the plain language of these claims and the teachings of the present specification.

In view of the foregoing remarks, reconsideration and withdrawal of this portion of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

B. The Recitation of "Variants and Derivatives Thereof"

In this rejection, the Examiner next contends that claim 6 is indefinite for reciting "variants and derivatives thereof," because the metes and bounds of "variants and derivatives" are allegedly unclear. By the foregoing amendments, claim 6 has been amended to specify that the claimed variants are those variants of the polypeptides recited in claim 6 that are "substantially reduced in RNAse H activity." As noted above, these amendments are fully supported in the specification as filed. This portion of the rejection therefore has been fully accommodated; reconsideration and withdrawal are therefore respectfully requested.

V. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at pages 3-6, sections 5-6, the Examiner has rejected claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, 32 and 41-43 under 35 U.S.C. § 103(a) as being unpatentable over Burmer, U.S. Patent No. 5,726,022 (Doc. Ref. AH1, of record; hereinafter "Burmer") in view of Carninci *et al.*, *Genomics 37*:327-336 (1996) (Doc. Ref. AR1, of record; hereinafter "Carninci"). Applicants respectfully traverse this rejection.

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In making this rejection, the Examiner first characterizes the disclosure of Burmer by contending that:

> Burmer discloses a method and kit to isolate nucleic acid sequences. The method involves using an adaptor which includes a restriction site and a ligand binding end ligated to the nucleic acid fragment of a first and second nucleic acid samples to provide the nucleic acid complementary to a primer for amplification (see column 4, lines 16-25). If the fragment of the second nucleic acid samples are amplified, the primers contain a ligand binding end (see column 4, lines 26-30). The isolation step is done by first removing the adaptors by restriction enzyme, capturing the nucleic acid containing the ligand and then the nucleic acid that were not captured is isolated (see column 2, lines 56-59). The ligand includes hapten (see column 7, line 4). The amplification is done by PCR, LCR and TAS (see column 8, lines 47-52). The solid support is described in column 7, lines 37-48.

Office Action at page 4, lines 4-13. The Examiner concludes that, based on this characterization, Burmer is an acceptable primary reference upon which to base a *prima facie* case of obviousness. *See* Office Action at pages 5-6. Applicants respectfully disagree with this conclusion.

Independent claim 1 (and thus the remaining claims which depend ultimately therefrom) is drawn to methods for producing nucleic acid molecules by: (a) mixing a template with (i) one or more polypeptides having polymerase activity and/or reverse transcriptase (RT) activity and (ii) a primer-adapter nucleic acid molecule which comprises one or more ligands and one or more cleavage sites; and (b) incubating the mixture of the template, polypeptide(s) and primer-adapter under conditions whereby a nucleic acid molecule is produced that (i) is complementary to all or a portion of the template and (ii) comprises the primer-adapter molecule. Hence, one key to the claimed methods is that the adapter molecule which has one or more ligands *and* one or more cleavage (*e.g.*, restriction) sites also serves as the *primer* molecule for synthesis of the first nucleic acid molecule.

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In contrast, the adaptors of Burmer are *not* used as primers for synthesis of a nucleic acid molecule. Instead, Burmer describes *ligating* double-stranded adaptors to nucleic acid fragments. Burmer therefore is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

Contrary to the Examiner's contentions, these deficiencies are not cured by the disclosure of Carninci. In characterizing this reference, the Examiner contends that:

> Carninci et al. disclose a method for efficiently constructing high-content full-length cDNA libraries. The method involves using a primer inserted with restriction sites, the restriction sites are incorporated into cDNA by PCR with ExTaq DNA polymerase and the amplified nucleic acid is cleaved by the restriction enzyme (see pg. 329, column 1-2, the fourth and fifth paragraph).

Office Action at page 4, paragraph 4. Based on this characterization, the Examiner concludes that the presently claimed invention would have been suggested to the ordinarily skilled artisan by the combination of Burmer and Carninci. *See* Office Action at pages 5-6. Applicants respectfully disagree with this conclusion.

As noted above, Burmer is seriously deficient as a primary reference. These deficiencies of Burmer are not cured by the disclosure of Carninci. As the Examiner has stated, Carninci relates to the use of primers having restriction sites. However, there is no disclosure or suggestion in Carninci that primers containing both cleavage sites *and* ligands should be used in the methods described in Carninci. In fact, the only disclosure of the use of ligands in Carninci is for the labeling of cap structures on eukaryotic mRNA, which simply permits the capture of mRNA molecules to facilitate subsequent production of full-length cDNA. *See* Carninci in the Abstract; at page 328, column 2 through page 329, column 1; and in Figure 1 at page 330. There is no disclosure in Carninci that would lead one of ordinary skill in the art to use a primer-adapter molecule containing both a ligand and a cleavage site for synthesis of a first nucleic acid molecule

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comprising the primer adapter (and thus comprising the ligand and cleavage site). Thus, Carninci provides no disclosure or suggestion that would cure the above-noted deficiencies of Burmer.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, this burden has not been satisfied, since Burmer and Carninci, alone or in combination, do not disclose or suggest the presently claimed invention. The skilled artisan therefore would not have been motivated to combine the disclosures of Burmer and Carninci to make and use the claimed invention with any reasonable expectation of success. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art"). Thus, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness of the claimed invention has not been established. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

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VI. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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